

5177052

SUBLINGUAL ALLERGEN-SPECIFIC IMMUNOTHERAPY IN ALLERGIC RHINITIS AND RELATED PATHOLOGIES: EFFICACY IN A PAEDIATRIC POPULATION

A. DELLA VOLPE, G.W. D'AGOSTINO, A.M. VARRICCHIO and N. MANSI

Otorhinolaryngology Department, Santobono-Pausilipon Pediatric Hospital, Naples, Italy

Received September 11, 2001 - Accepted November 23, 2001

The aim of this study was to demonstrate the efficacy and safety of the sublingual-swallow allergen-specific immunotherapy (SLIT) in a paediatric population suffering from allergic rhinitis and related pathologies. From March 1994 through March 2000, at our ENT Department 4000 children (1800 males and 2200 females), aged 3 to 14 years, were examined for recurrent nasal obstruction and nasal polyps. 2400 (60%) of them were allergic and underwent the following investigations: Impedance test, Pure tone audiometry, rhinomanometry, Prick test, RAST, nasal provocation test and paranasal sinus TC without contrast media. Of the allergic group we admitted 288 patients (12%) to a 3 yr SLIT, meeting the following criteria: children aged 5 years or more, mono-sensitised to one allergen and with family cooperation support. After three years of SLIT, we observed complete symptom remission and a marked improvement in instrumental examinations in 80% of these children. The improvement was poor in 8% of patients, while in 12% of the subjects no changes in symptoms and instrumental results were detected. These results are in agreement with previously published studies and confirm that SLIT can be a valid tool for treating allergic upper respiratory tract diseases in children.

Allergic diseases are becoming more and more relevant to otorhinolaryngologists, since many important upper airway diseases now recognise an allergic aetiology (1-2). Actually, it is possible to identify a role of allergy in the following diseases:

- Otitis Media (OM), in which the prevalence of nasal allergy ranges from 35 to 50% (3). In our experience such prevalence is about 38% (unpublished personal data).

- Sinusitis, a very frequent complication of allergic rhinitis. More than 50% of patients with allergic rhinitis shows abnormal sinus X-ray findings (4-6).

- Recurrent Upper Airway Infections (RRI). Allergy can be an important trigger. It has been shown that allergen exposure can induce the expression of Intercellular Adhesion-molecule-1 (ICAM-1): this molecule acting as a receptor for 90% of human rhinovirus, the expression of ICAM-

1 can raise the susceptibility of a patient to rhinovirus infections (7).

- Nasal Polyps, which very frequently appear in patients with intrinsic asthma, steroid-dependent asthma and ASA-intolerance (8).

In agreement with several Authors, we observed that the common symptoms of allergic rhinitis (nasal obstruction, rhinorrhea), together with the adverse effects of antihistamine medications, can lead to the cognitive retardation frequently reported in allergic children and adolescents (5). This observation led us to consider the prescription of allergen-specific immunotherapy (SIT) as a useful tool in the treatment of allergic upper airway diseases in paediatric patients, also with the aim of sparing antihistamines consumption in this age (9-10).

There is now an increasing body of evidence from academic studies to support the practice of

Key words: Allergen-specific immunotherapy, sublingual, upper respiratory tract diseases, children

Mailing address: Antonio della Volpe, MD
Santobono Pausilipon Pediatric Hospital
Via M. Fiori 6 - 80100 Naples - Italy
Ph.: 081-2205871; Fax: 081-2205871
E-mail: antoniodellavolpe@yahoo.it

0394-6320 (2002)

Copyright © by BIOLIFE, s.a.s.
This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder.
Unauthorized reproduction may result in financial and other penalties

sublingual-swallow immunotherapy (SLIT) (11-13), and the recently published WHO Position Paper approved by the leading Scientific Societies, stated that SLIT "may be a viable alternative" to the traditional subcutaneous therapy (14). Given these considerations, we believe that the sublingual route is painless, easier, and safer than the traditional injection SIT, could be especially indicated in the paediatric population and we prefer this route to treat our allergic patients. We present the results of a 3-yr SLIT treatment in a large survey of children with different upper respiratory tract diseases.

MATERIALS AND METHODS

Four thousand patients aged 3-14 years, 1800 males (45%) and 2200 females (55%) were observed in our ENT Department from March 1994 through March 2000. All patients had been previously followed in several ENT Departments for recurrent OM, sinusitis, nasal polyposis, recurrent respiratory infections and nasal obstruction not related to adenoid or tonsil hypertrophy, with concurrent mouth-breathing. All the patients underwent our investigation protocol, with the following interventions:

I LEVEL

- pure tone audiometry
- impedance test
- computerized anterior rhinomanometry

II LEVEL

- Prick test
- RAST test
- Specific nasal provocation test

III LEVEL

- Endoscopic examination of upper airways
- Sinuses computed tomography

Out of 4000 tested patients, 2400 subjects (60%) proved to be allergic.

Admission criteria to SLIT were the following:

- age > 5 years
- sensitization to only one allergen
- positive cooperation with patient's family and general paediatrician

Of the allergic subjects, 288 (12%) met our inclusion criteria and were included in the study. Patients were treated with allergen-specific immunotherapy by sublingual route. Hydroglyceric standardised extract

solutions (Allergopharma, Reinbek, Germany now represented by Merck, Milan, Italy) were employed. Treatment consisted of 3 vials containing 100 Therapeutic Units (TU)/ml, 1000 TU/ml, 10.000 TU/ml, respectively. Maintenance therapy was conducted using further vials of the higher concentration. SLIT was performed with a perennial maintenance schedule also with pollen extract. In the induction phase the treatment was administered daily, increasing the dosage every 3 days, starting with 1 drop a day up to 7 drops a day. The treatment was then carried out for 3 years, at the dosage of 7 drops every other day of the vial with higher concentration. Patients were instructed to maintain the drops sublingually for 2 minutes before swallowing. Gender distribution was 161 females (56%) and 127 males (44%); mean age was 9 years (3). Table I shows the distribution of the diseases.

Allergen sensitizations were first identified by Prick Test, and later confirmed by RAST Test and Specific Nasal Provocation Test with rhinomanometry performed before and after nasal provocation. Allergic sensitizations and subsequent SLIT compositions are shown in Tab. II.

Clinical and instrumental evaluations were necessarily different due to the different characteristics of the treated pathologies. Subjects with allergic rhinitis (102 pts, included 30 with nasal polyps) underwent rhinomanometry every month, and a RAST Test every 6 months. Subjects with recurrent OM (123 pts) underwent impedance test, audiometry and rhinomanometry every two months.

Patients with maxillary/ethmoid sinusitis (25 pts) were evaluated with rhinomanometry every two months and with endoscopy every six months, while a sinus CT was performed at the start and at the end of the treatment.

Patients with recurrent upper airways infections (33 pts) underwent routine blood tests, nasal smears examination and pharyngeal tampon. Rhinomanometry was also performed every two months.

Rhinomanometry

Anterior rhinomanometry measured the flow ratio, i.e. the ratio between expiratory and inspiratory air flow between the two nasal cavities. A normal flow ratio value is 1.

Outcome evaluation

Treatment outcomes were defined as follows:

- *complete remission*: complete absence of 3 symptoms (sneezing, rhinorrhea, nasal obstruction) along

with the complete normality of the instrumental examinations (computerized anterior rhinomanometry and impedance test);

-*decrease of symptoms*: absence of 2 out of 3 symptoms along with an improvement of the instrumental tests.

-*patients unchanged*: more than one symptom still present or no improvement in instrumental results.

In order to allow a more complete evaluation, we underline that some patients had also been operated (10 out of 82 with allergic rhinitis and/or nasal polyps, 7 out of 98 with OM and 2 out of 20 with sinusitis).

RESULTS

At the end of the study we were able to observe very positive results according to the outcome evaluation criteria: 229 patients (79.5 %) were in complete remission, while 27 patients (9.4%) showed a decrease of symptoms; the remaining 32 patients (11.1%) were unchanged. Table III reports the outcome evaluations taking into account the allergic sensitizations and the consequent SLIT compositions. Clinical results,

in term of percent of patients in clinical remission, improved or unchanged, were comparable among the four groups of different sensitizations. Similarly, Table IV reports the outcome according to the different clinical manifestations. Again, percent of patients in complete remission, improved or unchanged was comparable among patients with

Tab. I. Pathology distribution in treated patients.

No. OF PATIENTS	%	PATHOLOGY
102	35	allergic rhinitis (30 pts with nasal polyps)
123	43	recurrent OM
25	9	Ethmoid/maxillary sinusitis
38	13	recurrent upper airways infections

Tab. II. Allergic sensitizations and SLIT compositions.

ALLERGEN	No. OF PATIENTS	%
Dermatophagoides pteronyssinus	73	25
Dermatophagoides farinae	58	20
Parietaria	82	29
Grasses	75	26

Tab. III. Clinical results according to the relevant allergen.

No. OF PATIENTS	ALLERGEN	REMISSION	IMPROVEMENT	UNCHANGED
73	Dermat. Pter	57 (78%)	6 (9%)	10 (13%)
58	Dermat. Far.	46 (79%)	5 (9%)	7 (12%)
82	Parietaria	66 (80%)	10 (12%)	6 (8%)
75	Grasses	60 (80%)	6 (8%)	9 (12%)

Tab. IV. Clinical results according to treated pathologies.

No. OF PATIENTS	PATHOLOGY	REMISSION	IMPROVEMENT	UNCHANGED
102	Rhinitis, poliposis	82 (80%)	8 (8%)	12 (12%)
123	Recurrent OM	98 (79%)	10 (9%)	15 (12%)
25	Ethmoid/maxillary sinusitis	20 (80%)	2 (8%)	3 (12%)
38	R.R.I. of upper airways	26 (78%)	3 (10%)	4 (12%)

Tab. V. Rhinomanometry results (Flow-ratio) during SLIT in different pathologies.

	1st VISIT	6 MO	12 MO	18 MO	24 MO	30 MO	36 MO	p
SINUSITIS ALLERGIC RHINITIS	5.30±1.83	4.98±1.83	3.49±1.63	2.86±1.63	2.45±1.63	1.48±1.22	1.15±0.9	< 0.001
OTITIS	5.98±1.48	5.63±1.50	3.90±1.44	3.31±1.44	2.90±1.44	1.67±1.27	1.36±1.21	< 0.001
RRI	5.73±1.63	5.41±1.63	3.75±1.54	3.13±1.53	2.73±1.52	1.66±1.19	1.34±1.13	< 0.001
	5.37±1.73	5.05±1.73	3.47±1.57	2.85±1.56	2.44±1.56	1.56±1.15	1.29±1.10	< 0.001

Value are mean ± standard deviation.

rhinitis, OM, sinusitis and RRI. Among subjects in complete remission are listed all the patients who also underwent nasal surgery (again, 10 out of 82 with allergic rhinitis and/or nasal polyps, 7 out of 98 with OM and 2 out of 20 with sinusitis).

In Table V we report the Flow Ratio for each disease, as measured at six-month intervals during the 36 months of SLIT. Differences in the flow-ratio for each pathology at the start and after 3 years of SLIT were highly significant ($p < 0.001$). Figure 1 illustrates the decrease of Flow-ratio for each disease at every measurement. According with previous studies, we observed very few and mild side-effects, mainly related to the gastrointestinal tract. These effects were observed in a very small percentage of patients (2%). No patient had to withdraw from the treatment due to these effects.

DISCUSSION

SLIT has proved to be very effective and safe in our paediatric population, as already reported in many previously published studies. In controlled clinical trials, SLIT has been shown to be effective in reducing symptoms, medication scores and responses to provocation tests in patients allergic to mites (15-16), pollens (17-20), cat (21) and molds (22). Furthermore, in three studies comparing SLIT with injection therapy, results were shown to be comparable, and in another study even superior, to the traditional subcutaneous therapy (22-24), while a recent retrospective study showed a very high efficacy and tolerability of SLIT in 112 children under 12 years of age. (25). In our study,

very good results were actually observed either in pollen and house-dust mite sensitization, confirming that SLIT is effective in different allergen sensitizations.

All these studies also demonstrated that SLIT is actually easier, inexpensive, and safer to perform than subcutaneous therapy, as confirmed by post-marketing surveillance investigations. (25-26).

In our study, SLIT has also proved to be very safe: very mild adverse effects were observed in a small percentage of treated patients (2%). These effects were mainly localized to the gastrointestinal tract. Both, children and their parents were very satisfied with this route of therapy. We would also like to point out that to achieve successful treatment, good cooperation with the paediatrician and patient's family is required.

In our investigation, the efficacy of SLIT in ENT diseases is not only limited to "classic" allergic rhinitis, but was also effective in several other conditions involving the upper respiratory tract. Approximately 80 % of patients in all four groups of diseases attained "clinical remission" at the end of 3 years of SLIT, while a very small and comparable percentage of patients in all groups (8 to 13 %) reported no changes in clinical and instrumental evaluations. Symptomatic effectiveness was supported by the observation of improvement in rhinomanometry results, with Flow ratio reaching normal values by the end of treatment in all four groups of diseases.

In light of such evidence, our study demonstrates that an improvement of nasal respiratory compliance is associated with a lower incidence of ear and

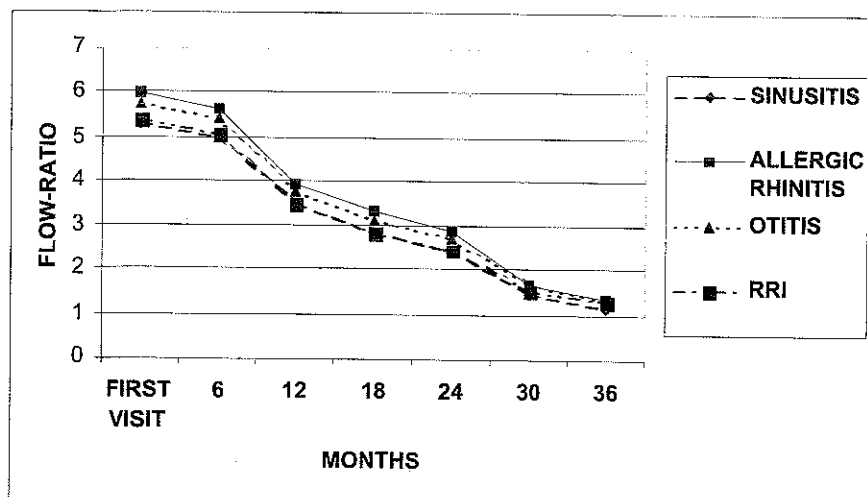


Fig. 1. Flow-ratio decrease during SLIT.

paranasal cavity flogistic events. These observations suggest that allergic mechanisms, besides the inflammation of Waldayer's lymphatic ring, have a role in the pathogenesis of upper respiratory tract diseases such as recurrent otitis media and sinusitis.

These results have usually been observed in allergen-specific immunotherapy of allergic rhinitis, where clinical effectiveness has been repeatedly confirmed (27).

Upper respiratory involvement can be a frequent complication of allergic rhinitis (28), but can also be observed with no evidence of this disease, and several lines of strong evidence support causality between atopy and upper respiratory diseases. This link with atopy has been actually reported in OM, nasal polyps, sinusitis and recurrent respiratory infections (29-32).

Some studies have addressed the anti-allergic medical treatment of these conditions with contrasting results (33-34), but very few investigations have been carried out to evaluate the role of allergen-specific immunotherapy in upper respiratory tract diseases other than allergic rhinitis (35-37).

We have performed such an evaluation in a large number of patients and found that, even in an open, uncontrolled study design, sub-lingual allergen-specific immunotherapy was clinically very effective in all the upper respiratory tract diseases characterized by a significant atopic component.

Because of this useful therapeutic option, an appropriate evaluation^a for underlying allergies may therefore be indicated in any patient with chronic upper respiratory tract symptoms.

REFERENCES

1. **Warner J.O.** 1997. Early treatment of the atopic child. *Paediatric Allergy Immunol.* 8:46.
2. **Wright A.L., C.G. Holberg and F.D. Martinez.** 1994. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Paediatrics* 94:89.
3. **Fireman P.** 1997. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. *J. Allergy Clin. Immunol.* 99:S 787.
4. **Furukawa C.T.** 1992. The role of allergy in sinusitis in children. *J. Allergy Clin. Immunol.* 90:515.
5. **Marshall P.S. and E.A. Colon.** 1993. Effects of allergy season on mood cognitive functions. *Ann. Allergy* 71:251.
6. **Minotti D.A.** 1994. Allergic Rhinitis and sinusitis. *Immunol. Allergy Clin. N. Am.* 14:113.
7. **Sigman K. and B. Mazer.** 1996. Immunotherapy for children asthma: is there a rationale for its use? *Ann. Allergy Asthma Immunol.* 76:299.
8. **Jordana M., J. Dolovich, J. Ohno, et al.** 1995. Nasal polyposis model for chronic inflammation. In *Asthma and rhinitis*. W.E. Busse, S.T. Holgate, ed. Blackwell Scientific Publication Boston, p.156.
9. **Bousquet J., M. Bullinger et al.** 1994. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J. Allergy Clin. Immunol.* 94:182.
10. **La Rosa M., S. Leonardi, G. Marchese, A. Corrias, G. Barberio, N. Oggiano and I. Grimaldi.** 2001. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children. *Ann. Allergy Asthma Immunol.* 87:48.
11. **Frew A.J. and H.E. Smith.** 2001. Sublingual immunotherapy. *J. Allergy Clin. Immunol.* 107:441.
12. **Holt P., P.D. Sly and W. Smith.** 1998. Sublingual immunotherapy for allergic respiratory disease. *Lancet* 351:613.
13. **Malling H.J., J. Abreu-Noguiera, B. Alvarez-Cuesta et al.** 1998. Local immunotherapy. *Allergy* 53:933.
14. **Bousquet J., R.F. Lockey and H.G. Malling.** 1998. WHO Position Paper. Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases. *Eur. J. Allergy Clin. Immunol.* 53:1.
15. **Pajno G.B., L. Morabito, G. Traina, et al.** 1998. Clinical and immunological effects of a long-term sublingual immunotherapy to mite in asthmatic children. A double blind study. *J. Allergy Clin. Immunol.* 101(S):100.
16. **Passalacqua G., M. Albano, L. Fregonese, et al.** 1998. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 351:629.
17. **Horak F., P. Stubner, U.E. Berger, B. Marks, J. Toth and S. Jager.** 1998. Immunotherapy with sublingual birch pollen extract. A short-term double-blind placebo study. *J. Investig. Allergol. Clin. Immunol.* 8:165.
18. **Hordijk G.J., J.B. Antvelink and R.A. Luwema.** 1998. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. *Allergol. Immunopathol.* 26:234.
19. **Vourdas D., E. Syrigou, P. Potamianou, F. Carat, T. Batard, C. Andre and P.S. Papageorgiou.** 1998. Double-blind, placebo-controlled evaluation of sublingual

- immunotherapy with standardized olive pollen extract in paediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 53:662.
20. **La Rosa M., C. Ranno, C. André, et al.** 1999. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J. Allergy Clin. Immunol.* 104:425.
 21. **Nelson H.S., J. Oppenheimer, G.A. Vatsia and A. Buchmeier.** 1993. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J. Allergy Clin. Immunol.* 92:229.
 22. **Bernardis P., M. Agnoletto, P. Puccinelli, S. Parmiani and M. Pozzan.** 1996. Injective versus sublingual immunotherapy in *Alternaria tenuis* allergic patients. *J. Investig. Allergol. Clin. Immunol.* 6:55.
 23. **Mungan D., Z. Misirligil and L. Gurbuz.** 1999. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma—a placebo controlled study. *Ann. Allergy Asthma Immunol.* 82:485.
 24. **Quirino T., E. Iemoli, E. Siciliani, S. Parmiani and F. Milazzo.** 1996. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin. Exp. Allergy* 26:1253.
 25. **Madonini E., F. Agostinis, R. Barra et al.** 2000. Safety and efficacy evaluation of sublingual allergen-specific immunotherapy. A retrospective, multicenter study. *Int. J. Immunopathol. Pharmacol.* 13:77.
 26. **Almagro E., O. Asensio, J.M. Bartolome et al.** 1995. Multicenter drug surveillance of sublingual immunotherapy in allergic patients. *Allergol. Immunopathol.* 23:153.
 27. **Ross R.N., H.S. Nelson and I. Finegold.** 2000. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin. Ther.* 22:342.
 28. **Skoner D.P.** 2000. Complications of allergic rhinitis. *J. Allergy Clin. Immunol.* 105:S605.
 29. **Skoner P.D. and M.L. Casselbrant.** 1998. Otitis Media. In: *Allergy. Principles and practice.* E. Middleton jr, C.E. Reed, E.F. Ellis, N.F. Adkinson, J.W. Yungingerr, W.W. Busse ed. Mosby-Year Book Inc., p. 1036.
 30. **Asero R. and G. Bottazzi.** 2001. Nasal polyposis: a study of its association with airborne allergen hypersensitivity. *Ann. Allergy Asthma Immunol.* 86:283.
 31. **Van Cauwenberge P. and J.B. Watelet.** 2000. Epidemiology of chronic rhinosinusitis. *Thorax* 55(S):20.
 32. **Lester M.R. and L.C. Schneider.** 2000. Atopic diseases and upper respiratory infections. *Curr. Opin. Pediatr.* 12:511.
 33. **Flynn C.A., G. Griffin and F. Tudiver.** 2001. Decongestants and antihistamines for acute otitis media in children (Cochrane Review). *Cochrane Database Syst. Rev.* 2:CD001727.
 34. **Fireman P.** 1990. The role of antihistamines in otitis. *J. Allergy Clin. Immunol.* 86:638.
 35. **Asakura K., T. Kojima, H. Shirasaki and A. Kataura.** 1990. Evaluation of the effects of antigen specific immunotherapy on chronic sinusitis in children with allergy. *Auris Nasus Larynx* 17:33.
 36. **Hurst D.S.** 1990. Allergy management of refractory serous otitis media. *Otolaryngol. Head Neck Surg.* 102:664.
 37. **Nishioka G.J., P.R. Cook, W.E. Davis and J.P. McKinsey.** 1994. Immunotherapy in patients undergoing functional endoscopic sinus surgery. *Otolaryngol. Head Neck Surg.* 110:406.